REMARKS

Claims 41-62 are pending in the application and have been rejected. Claims 41-62 have been amended. Reconsideration and allowance of Claims 41-62 in view of the above amendments and following remarks is respectfully requested.

The Claimed Invention as Amended

The pending independent claims are directed to methods for treating a condition or disease in a warm-blooded animal. Each independent method claim recites the step of administering to a warm-blooded animal an effective amount a HMG-CoA reductase inhibitor.

As amended, Claim 41 is directed to a method for increasing adiponectin production that includes administering one or more HMG-CoA reductase inhibitor(s). Claims 43-47, 57, 59, and 61 depend from Claim 41.

As amended, Claim 42 is directed to a method for treating Syndrome X or metabolic syndrome that includes administering a composition consisting essentially of one or more HMG-CoA reductase inhibitor(s). Claim 57 depends from Claim 42.

As amended, Claim 48 is directed to a method for treating hypoadiponectinemia that includes administering one or more HMG-CoA reductase inhibitor(s). Claims 55-57, 61, and 62 depend from Claim 48.

As amended, Claims 49, 50, 51, and 52 are directed to methods for improving insulin resistance, treating hypertension, treating obesity, and treating arteriosclerosis, respectively. Each of these claims recites the step of administering a composition consisting essentially of one or more HMG-CoA reductase inhibitor(s). Claims 55-57, 61, and 62 depend from Claims 49-52.

As amended, Claim 53 is directed to a method for treating diabetes, diabetes complications, hypertension, obesity, or arteriosclerosis caused by hypoadiponectinemia, that includes the step of administering a composition consisting essentially of one or more HMG-CoA reductase inhibitor(s). Claims 55-58, 61, and 62 depend from Claim 53.

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As amended, Claim 54 relates to a method for treating hypertension, obesity, or arteriosclerosis caused by insulin resistance syndrome that includes the step of administering a composition consisting essentially of one or more HMG-CoA reductase inhibitor(s). Claims 55-57, 61, and 62 depend from Claim 54.

The Rejection of Claims 41 and 43-47 Under 35 U.S.C. § 112, Second Paragraph

Claims 41 and 43-47 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

According to the Examiner, the term "enhancement" in Claim 41 and in the specification is not defined. Without acquiescence to the Examiner's rejection, Claim 41 has been amended to recite "A method for increasing adiponectin production." Support for the amendment can be found throughout the specification as originally filed. Withdrawal of the rejection is requested.

Claims 43-47, and 59-61 have been rejected as not being in proper dependent format. Claims 43-47, and 55-60 have been amended placing these claims in proper format.

The Rejection of Claims 41-62 Under 35 U.S.C. § 112, First Paragraph

Claims 41-62 have been rejected under 35 U.S.C. § 112, first paragraph, for failing to enable the skilled person to use the invention commensurate in scope with the claims.

As an initial matter, the Examiner believes that the application fails to enable the "prevention" (i.e., prophylaxis) of any disease or condition. Without acquiescence to the Examiner's rejection, independent Claims 42, 48, 50, 51, 53, and 54 have been amended to recite a method for treatment (not prophylaxis) of the specified disease or condition.

The Examiner is of the opinion that the specification fails to teach how to determine and select the population of individuals with or without hypoadiponectinemia, metabolic syndrome, diabetes, and complications thereof for treatment. According to the Examiner, it is not clear what parameters one skilled in the art would use in order to identify a subject in which the disease could be prevented. In addition, the Examiner states that there is insufficient evidence in

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the specification that the diseases identified in the claims would be inhibited with the administration with one or more of HMG-CoA reductase inhibitors. Applicants respectfully disagree.

Applicants note that the diseases recited in Claims 41-62, such as hypoadiponectinemia, metabolic syndrome, diabetes, and complications thereof, are well-known diseases/conditions that are readily identified and diagnosed by a person skilled in the art (i.e., a medical doctor in the relevant field). The application has provided sufficient support for the inhibitory effect of HMG-CoA reductase inhibitors on the diseases recited in Claims 41-62, as evidenced by Example 1, "Adiponectin production enhancing action (in vitro)," and Example 2, "Adiponectin production enhancing action (in vivo) and glucose uptake enhancing action." Furthermore, M.P.E.P. 2164.02 titled "Working Example" allows the correlation between *in vitro* and *in vivo* animal model assays and a claimed method of use "if the art is such that a particular model is recognized as correlating to a specific condition."

To assist the Examiner in further understanding the state of the art (the knowledge of the skilled person) and the relationship between adiponectin and diseases, applicants provide two recent publications: (1) Pathophysiological significance of adiponectin, Shimomura et al., *Med Mol Morphol* 2007 40:55-67, attached as **Exhibit A**; and (2) Adiponectin and Cardiovascular Disease, Han et al., *J Am Coll Cardiol* 2007 49:531-538, attached as **Exhibit B**.

The Shimomura publication shows the clinical significance of adiponectin and the relationship between adiponectin and several diseases (obesity, cardiovascular disease, hypertension and dyslipidemia, metabolic syndrome, inflammation, cancer and other diseases). See pages 58 and 59. The Han publication describes the relationship between adiponectin and cardiovascular disease.

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As evidenced by these publications, the skilled person would understand that the experimental results set forth in the application as originally filed establish the correlation between the *in vitro* and *in vivo* animal model assays in the application and the claimed methods.

Because the application as originally filed provides a disclosure that enables the skilled person to make and use the claimed invention, the application satisfies the enablement requirement. Withdrawal of the rejection is requested.

The Rejection of Claims 41-62 Under 35 U.S.C. § 103(a)

Claims 41-62 have been rejected under 35 U.S.C. § 103(a) as being unpatentable as obvious over the combined teaching of U.S. Patent No. 6,130,214, issued to Lohray et al., in view of U.S. Patent No. 6,384,062, issued to Ikeda et al. The Examiner also refers to Schulze et al., "Adiponectin and Future Coronary Heart Disease Events Among Men With Type 2 Diabetes", *Diabetes 54*:534-539, 2005, printed pages 1-6.

Each of Claims 41-62 have been amended. Of Claims 41-62, Claims 41, 42, and 48-54 are independent claims. Claims 43-47, 57, 59, and 61 depend from Claim 41. Claim 57 depends from Claim 42. Claims 55-57, 61, and 62 depend from Claim 48. Claims 55-57, 61, and 62 depend from Claims 49-52. Claims 55-58, 61, and 62 depend from Claim 53. Claims 55-57, 61, and 62 depend from Claim 54.

The Cited References. The Lohray reference relates to antiobesity and hypocholesterolemic compounds. Specifically, the Lohray reference discloses novel β-aryl-α-oxysubstituted alkylcarboxylic acids (benzothiazin and benzoxazin derivatives) of the general formula (I):

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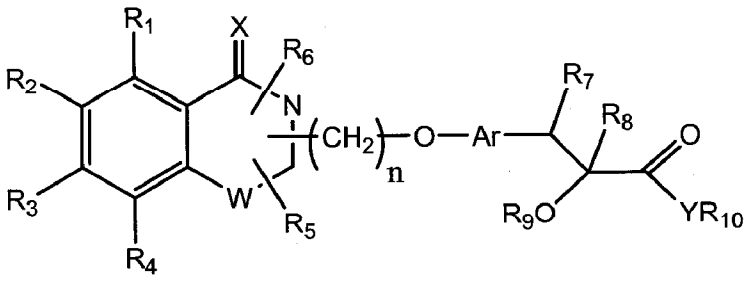

(I)

The Lohray reference states at Col. 2, lines 1-3, that its compounds, in combination with one or more HMG-CoA reductase inhibitors, are useful in the treatment and/or prophylaxis of a variety of diseases.

The Ikeda reference relates to pharmaceutical compositions that include an insulin sensitivity enhancer in combination with other antidiabetics (e.g., a HMG-CoA reductase inhibitor such as pravastatin) that differ from the enhancer in the mechanism of action. The compositions show a depressive effect on diabetic hyperglycemia and are useful for prophylaxis and treatment of diabetes and diabetes complications.

The Schulze reference relates to the relationship between adiponectin and the future coronary heart disease (CHD) events among men with Type 2 diabetes and describes the association between plasma adiponectin levels and incidence of CHD. The results set forth in the reference suggest that increased adiponectin levels are associated with moderately decreased CHD risk in men.

The Lohray and Ikeda references each describe administering a HMG-CoA reductase inhibitor or a statin in combination with a second therapeutic drug to treat a condition: the Lohray reference describes administering one or more HMG-CoA reductase inhibitors in combination with a novel benzothiazin or benzoxazin derivative to treat a variety of conditions; and the Ikeda reference describes administering a statin (a HMG-CoA reductase inhibitor) in combination with a novel insulin sensitivity enhancer compound to treat diabetes and diabetes complications.

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Independent Claims 42, and 49-54. Claims 42, and 49-54 have been amended to recite that the specified diseases/conditions are treated by administering a composition consisting essentially of one or more water-soluble HMG-CoA reductase inhibitor(s). The amendments to Claims 42 and 49-54 narrow the scope of the compositions administered in the methods to those that include one or more HMG-CoA reductase inhibitors and exclude from the administered compositions any other components that would materially affect the properties of the composition. By these amendments, combination administrations, such as described in the Lohray and Ikeda references, are excluded from the scope of the amended claims.

In view of the amendments to Claims 42, and 49-54, withdrawal of the rejection of Claims 42, 49-58, 61, and 62 is requested.

Independent Claims 41 and 48. Claims 41 and 48 are directed to methods for increasing adiponectin production and hypoadiponectinemia, respectively. Each method includes the step of administering an effective amount of one or more HMG-CoA reductase inhibitor(s) to a warm-blooded animal in need of such treatment. Claim 48 further recites that the HMG-CoA reductase inhibitor is water soluble.

Neither the Lohray nor Ikeda references describes, teaches, or suggests in any way a method for either increasing adiponectin production or treating hypoadiponectinemia.

As noted above, the Lohray reference describes novel β-aryl-α-oxysubstituted alkylcarboxylic acids for use in the treatment of hypertension, coronary heart disease, atherosclerosis, stroke, peripheral vascular diseases, familial hypercholesterolemia, hyperglyceridemia, lowering of atherogenic lipoproteins, very low density lipoprotein, and LDL, renal diseases including glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, and nephropathy, insulin resistance, leptin resistance, impaired glucose tolerance, dyslipidemia, disorders related to syndrome X such as hypertension, obesity, insulin resistance, coronary heart disease, and other cardiovascular disorders, improving cognitive functions in

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dementia, treating diabetic complications, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome, inflammatory bowel diseases, osteoporosis, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma, and cancer (see Col. 1, lines 43-67). The reference also states that the novel compounds are useful in the treatment of those diseases in combination with one or more HMG-CoA reductase inhibitors (see Col. 2, lines 1-3).

As noted above, the Ikeda reference describes pharmaceutical compositions that include an insulin sensitivity enhancer in combination with other antidiabetics that differ from the enhancer in the mechanism of action for use in treating diabetes and diabetes complications including diabetic neuropathy, nephropathy, retinopathy, macroangiopathy, and osteopenia (see Col. 18, lines 1-6).

Neither reference describes, teaches, or suggests the inventions as now claimed: a method for increasing adiponectin production or a method for treating hypoadiponectinemia that includes the step of administering one or more HMG-CoA reductase inhibitor(s).

According to the Examiner, the Schulze reference discloses adiponectin as a major modulator of insulin resistance and dyslipidemia, mechanisms that are associated with increased atherosclerotic risk in diabetic patients. The Examiner states that the claimed invention relates to HMG-CoA reductase inhibitors as effective agents against dyslipidemia. The Examiner then concludes that, by virtue of the mechanism of action of agents, adiponectin is <u>likely</u> to increase with HMG-CoA reductase inhibitors treatment. Applicants respectfully disagree.

Applicants respectfully submit that the Examiner has failed to provide or establish any link between adiponectin production and HMG-CoA reductase inhibitors in the methods of the claimed invention. Should the Examiner maintain the position that there is a link between adiponectin production and HMG-CoA reductase inhibitors, applicants respectfully request that the Examiner provide evidence (i.e., one or more publications) demonstrating the link. The Schulze reference, directed to the relationship between adiponectin and future coronary heart

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disease (CHD) events among men with Type 2 diabetes and the association between plasma adiponectin levels and incidence of CHD, fails to establish the link.

Applicants believe that the present application is the first demonstration that administration of HMG-CoA reductase inhibitors increases adiponectin production and is effective in treating hypoadiponectinemia.

Because the cited references fail to teach or suggest a method for increasing adiponectin production (Claim 41) or a method for treating hypoadiponectinemia (Claim 48), applicants submit that the claimed invention is non-obvious and patentable over the cited references. Withdrawal of the rejection of Claims 41, 43-48, 55-57, and 59-62 is requested.

Conclusion

In view of the above amendments and foregoing remarks, Claims 41-62 are believed to be in condition for allowance. If any issues remain that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1755.

Respectfully submitted,

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